Clinical Impact of Rapid Drug Susceptibility Testing to Accompany Fluoroquinolone-Containing Universal Tuberculosis Regimens: A Markov Model

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Background. To appropriately treat tuberculosis (TB) with regimens that combine novel and older drugs, evidence-based, context-specific strategies for drug-susceptibility testing (DST) will be required.

Methods. We created a Markov state-transition model of 100 000 adults with TB receiving a novel, fluoroquinolone (FQ)-containing regimen. We estimated clinical outcomes and resource utilization with no FQ-DST, universal FQ-DST, or FQ-DST only for patients with rifampin-resistant TB ("targeted FQ-DST"). We considered scenarios of stronger (South Africa) and weaker (Southeast Asia) correlation of fluoroquinolone resistance with rifampin resistance, with sensitivity analysis for other setting and regimen characteristics.

Results. Relative to no FQ-DST, targeted FQ-DST increased cure of FQ-resistant TB by 7.5% (interquartile range [IQR], 6.7%–9.2%) in South Africa and 1.7% (IQR, 0.7%–2.5%) in Southeast Asia. However, rare FQ resistance among the more prevalent rifampin-susceptible TB accounted for 50% of FQ-resistant TB in South Africa and 83% in Southeast Asia. As a result, universal FQ-DST further increased cure of FQ-resistant TB by 3.4% (IQR, 2.3%–5.4%) in South Africa and 5.8% (IQR, 5.1%–6.3%) in Southeast Asia. With targeted FQ-DST, 1 additional patient was cured per 50 (IQR, 42–70) tests in South Africa and 44 (IQR, 37–51) in Southeast Asia. When expanding from targeted to universal FQ-DST, 1 additional cure required 3500 (IQR, 2300–5500) tests in South Africa and 410 (IQR, 370–450) in Southeast Asia.

Conclusions. FQ-DST improved patient outcomes and was particularly important for high-risk patient groups and less robust regimens. A universal strategy was favored in generalized epidemics of fluoroquinolone resistance.

Keywords. tuberculosis treatment; drug susceptibility testing; epidemiology of drug resistance; fluoroquinolones; modeling.

Regimen development is reshaping the treatment of drug-resistant tuberculosis (TB), and forthcoming regimens could allow nearly all patients, including those with TB resistant to current first-line drugs, to receive the same treatment (ie, a universal regimen). These changes also create a need for new drug susceptibility testing (DST) strategies [1–3]. Adding to the challenge, a number of potential regimens pair novel drugs with existing TB drugs (such as pyrazinamide and fluoroquinolones) to which substantial resistance already exists, but DST is not yet widely performed [4–10]. The extent, distribution, and correlation of resistance to existing TB drugs can vary considerably between settings. For example, in sub-Saharan Africa, resistance to fluoroquinolones tends to be heavily concentrated among

strains of *Mycobacterium tuberculosis* that are also resistant to rifampin, whereas in much of Asia (where fluoroquinolone use and fluoroquinolone-resistant bacteria are more widespread [11]), fluoroquinolone resistance is also sufficiently common among rifampin-susceptible TB (RS-TB) strains that most fluoroquinolone-resistant TB is rifampin-susceptible [10, 12, 13]. As TB programs consider adoption of new regimens, they need corresponding approaches to DST that are appropriate for their local epidemiology and align with available resources.

One novel regimen that can illustrate the DST considerations that will accompany a fluoroquinolone-containing novel regimen is the "BPamZ" regimen consisting of bedaquiline (B), pretomanid (Pa), the fluoroquinolone moxifloxacin (M), and pyrazinamide (Z). This drug combination has performed well compared to the standard first-line TB regimen in animal and early human studies [14, 15], and it is currently being evaluated as a treatment-shortening regimen for both RS-TB and rifampin-resistant TB (RR-TB) in the phase 2c/3 SimpliciTB trial [7]. In patients with fluoroquinolone-resistant TB, such a regimen will provide less treatment-shortening potential and less protection against acquisition of resistance, and coexisting

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resistance to companion drugs such as pyrazinamide (leaving at most 2 effective drugs) will further worsen outcomes. Recent advances in rapid molecular DST could facilitate widespread implementation of FQ-DST alongside a novel regimen. The Xpert XDR cartridge (Cepheid Inc, Sunnyvale, California), expected in 2020, would allow near-patient molecular FQ-DST using the same GeneXpert platform widely used for TB diagnosis and rifampin susceptibility testing [16]. The FluoroType XDR assay (Hain Lifescience, Nehren, Germany) could allow for more centralized but similarly rapid FQ-DST [17].

There are multiple potential approaches to implementing FQ-DST in conjunction with a novel, fluoroquinolone-containing regimen. One would be to perform up-front FQ-DST for all people diagnosed with TB. This approach is the costliest but may result in the best outcomes for patients. Another option would be to perform FQ-DST using a staged approach, by first evaluating patients for some other characteristic (eg, resistance to rifampin) that is associated with fluoroquinolone resistance and is widely tested; only those found to be at higher risk would then be eligible for FQ-DST [18]. This approach may achieve similar outcomes as the first with fewer tests performed, but requires a 2-step testing procedure and misses some drug resistance. Finally, a cost-saving—but also likely least effective—option would be to forego FQ-DST altogether, potentially using other available data to infer likely resistance profiles.

The optimal DST approach is likely to vary depending on the regimen, patient population, and resources available. As novel TB drug regimens near approval and scale-up, it is important to quantify the tradeoffs between these approaches. We therefore developed a Markov model to compare options for FQ-DST when introducing a novel, fluoroquinolone-containing treatment regimen for RS-TB and RR-TB, using the BPamZ drug combination as an illustrative example. We focus on 2 settings (South Africa and the Southeast Asian region) with large TB epidemics that differ in the degree to which resistance to rifampin overlaps with resistance to fluoroquinolones.

METHODS

We developed Markov models of representative cohorts of individuals with undiagnosed prevalent TB in South Africa and Southeast Asia, building on previous work [19] and described in full in the Supplementary Methods, including [Supplementary Tables 1–7](#). In brief, each individual proceeded through diagnosis and treatment (potentially, multiple rounds) until cure was attained or death occurred ([Figure 1](#)). The initial characteristics within each cohort were drawn from notifications to national programs [20, 21] and population-representative drug resistance surveys [10, 22, 23]. Individuals were characterized according to TB status, prior TB treatment, human immunodeficiency virus infection, smear status at time of diagnosis, and TB drug resistance (to each of rifampin, isoniazid,

pyrazinamide, moxifloxacin, bedaquiline, and pretomanid, accounting for correlated resistance between drugs).

Treatment outcomes were modeled as a function of the drugs used in the treatment regimen, the patient's TB drug resistance phenotype, and the duration of treatment completed (accounting for possible loss to follow-up). We modeled BPamZ as an illustrative novel regimen. Because trials of cure are still under way, we used observed proportions of patients achieving culture conversion after 8 weeks of treatment with BPamZ (or with subsets such as BPaZ) [15] as the basis for projecting probabilities of cure for each possible combination of effective drugs received and treatment months completed [24]. Our projections assumed (in accordance with SimpliciTB trial design) that a 4-month regimen of BPamZ was as likely to cure pan-susceptible TB as 6 months of the current first-line regimen [7]. We also modeled acquisition of resistance to drugs in the treatment regimen, with probabilities dependent on the initial resistance profile.

Primary analyses considered cohorts from South Africa and the Southeast Asian region ([Table 1](#)), estimating pyrazinamide and moxifloxacin resistance from pooled survey data from 2 sites in South Africa [10] or from national surveys in Bangladesh [10], Pakistan [10], and India [22]. We incorporated low- and high-degree moxifloxacin resistance [25] and all correlations between rifampin, pyrazinamide, and moxifloxacin resistance [26]. We assumed that 90% of patients underwent Xpert MTB/RIF testing prior to treatment. To simplify interpretation of generalizable principles, primary analyses assumed 4 months of BPamZ as first-line treatment for both RS-TB and RR-TB. A sensitivity analysis (mirroring the SimpliciTB protocol) modeled an increase to 6 months of BPamZ for patients with RR-TB, to compensate for their higher risk of pyrazinamide resistance [7].

We compared 3 DST implementation approaches: (1) no FQ-DST; (2) FQ-DST only after rifampin resistance was detected ("targeted FQ-DST"); or (3) FQ-DST for all patients ("universal FQ-DST").

We assumed FQ-DST would have the sensitivity preliminarily reported for Xpert XDR [16]. When moxifloxacin resistance was detected, we assumed that regimen adjustments—for example, addition of drug(s) such as linezolid or increasing the moxifloxacin dose [27, 28]—would restore the same probability of cure that the patient would have received from BPamZ in the absence of moxifloxacin resistance.

Outcomes included the proportion of individuals cured by treatment; time with active TB; and number of DST tests performed. We simulated these outcomes repeatedly for a cohort of 100 000 individuals with TB in each setting and reported the median and interquartile range (IQR) across 50 repetitions. These IQRs thus reflect probabilistic but not parameter uncertainty.

To assess the impact of parameter uncertainty, we performed 1-way sensitivity analyses for all model parameters.

Table 1. Characteristics of Simulated Cohorts of Patients With Tuberculosis in South Africa and Southeast Asia

Characteristic	South Africa	Southeast Asia
Cohort characteristic		
Rifampin resistance prevalence	Moderate	Moderate
Moxifloxacin and pyrazinamide resistance prevalence, overall	Low	Moderate
Correlation between rifampin resistance and moxifloxacin/pyrazinamide resistance	High	Low
Select setting-specific input parameters		
Probability of rifampin resistance		
If treatment naive	3.4%	2.8%
If previously treated	7.1%	13%
Probability of moxifloxacin resistance ^a		
If rifampin resistant	10%	15%
If rifampin susceptible	0.4%	3.6%
Probability of pyrazinamide resistance ^a		
If rifampin resistant	44%	29%
If rifampin susceptible	1.3%	5.1%
Resulting % of cohort with:		
Rifampin-resistant TB	3.8%	4.5%
Moxifloxacin-resistant TB	0.8%	4.1%
Moxifloxacin- and rifampin-resistant TB	0.4%	0.7%
Moxifloxacin-resistant, rifampin-susceptible TB	0.4%	3.4%
Pyrazinamide-resistant TB	2.9%	6.2%
Pyrazinamide-, moxifloxacin-, and rifampin-resistant TB	<0.1%	0.4%
Pyrazinamide- and moxifloxacin-resistant, rifampin-susceptible TB	0.3%	0.3%

Abbreviation: TB, tuberculosis.

^aCorrelation between moxifloxacin and pyrazinamide resistance is also modeled, with odds ratio 2.88.

89.2% (IQR, 89.1%–89.3%) of patients who initiated treatment in both South Africa and Southeast Asia (Table 2). These outcomes were better than those projected for the current standard of care, with much of the benefit (a >20% increase in probability of cure) experienced by patients with

RR-TB (Table 2). The probability of cure among patients with moxifloxacin-resistant (MFX-R) TB, however, was only 73.8% (72.8%–75.3%) in South Africa and 81.1% (80.7%–81.4%) in Southeast Asia, no better than outcomes under standard-of-care regimens (Table 2).

RR-Targeted FQ-DST: Expected Impact on TB Cure

Implementation of FQ-DST for people with diagnosed RR-TB in South Africa resulted in a 15.2% increase (IQR, 12.6%–16.6%) in the proportion of MFX-R, RR-TB that was cured by the initial treatment attempt (an increase in the median proportion cured from 66.6% to 81.4%). This corresponded to a 1.9% (IQR, 1.1%–2.4%) increase in cure of RR-TB overall and a 7.5% (IQR, 6.7%–9.2%) increase in cure of MFX-R TB overall. In Southeast Asia, RR-targeted FQ-DST similarly increased cure of MFX-R, RR-TB by 12.4% (IQR, 11.2%–13.6%), and cure of all RR-TB by 2.3% (IQR, 1.9%–2.8%), but cure of all MFX-R TB by only 1.7% (IQR, 0.7%–2.5%) (Table 2). Time with potentially infectious fluoroquinolone-resistant TB or RR-TB was correspondingly reduced (Supplementary Tables 8 and 9).

The number of FQ-DSTs needed to effect 1 additional cure was comparable in these 2 settings: 50 (IQR, 43–62) in South Africa and 45 (IQR, 38–53) in Southeast Asia. Both settings have similar burdens of RR-associated fluoroquinolone and pyrazinamide resistance; South Africa has a slightly lower prevalence of moxifloxacin resistance among RR-TB (which increases the number of DSTs required to detect a moxifloxacin-resistant case), but a higher risk of accompanying pyrazinamide resistance (which increases the harm of failing to detect moxifloxacin resistance) (Table 3).

Universal FQ-DST: Projected Incremental Impact

A large proportion of moxifloxacin resistance (83% in Southeast Asia and 50% in South Africa) occurs among RS-TB, although the prevalence of MFX-R is much lower among RS-TB (Table 1).

Table 2. Projected Proportion of Patients Cured by Initial Course of Tuberculosis Treatment, According to Regimen and Drug Susceptibility Testing Approach

Country and Approach	Current SOC (Conventional Regimens for RS-TB and RR-TB)	Novel Regimen for All, With No FQ-DST	Novel Regimen, With Targeted FQ-DST (for RR-TB only)	Novel Regimen, With Universal FQ-DST
South Africa				
Full cohort	87.5% (87.4%–87.6%)	89.2% (89.1%–89.3%)	89.3% (89.2%–89.4%)	89.4% (89.4%–89.5%)
RS-TB	88.4% (88.2%–88.4%)	89.4% (89.3%–89.4%)	89.4% (89.3%–89.5%)	89.5% (89.4%–89.7%)
RR-TB	65.3% (64.8%–65.8%)	85.4% (84.9%–85.8%)	86.9% (86.6%–87.4%)	87.0% (86.7%–87.6%)
MFX-R TB	74.2% (72.8%–75.3%)	73.8% (72.8%–75.3%)	81.6% (80.4%–82.9%)	85.7% (84.9%–86.5%)
Southeast Asia				
Full cohort	87.0% (86.9%–87.1%)	89.2% (89.1%–89.3%)	89.3% (89.2%–89.3%)	89.5% (89.4%–89.6%)
RS-TB	88.4% (88.3%–88.5%)	89.4% (89.3%–89.4%)	89.3% (89.3%–89.4%)	89.6% (89.5%–89.6%)
RR-TB	59.3% (59.0%–59.7%)	86.0% (85.7%–86.5%)	88.2% (87.9%–88.6%)	88.1% (87.9%–88.5%)
MFX-R TB	82.6% (82.1%–83.0%)	81.1% (80.7%–81.4%)	82.8% (82.4%–83.4%)	88.7% (88.4%–89.0%)

Data are presented as percentage (interquartile range) of patients cured.

Abbreviations: DST, drug susceptibility testing; FQ, fluoroquinolone; MFX-R, moxifloxacin-resistant; RR, rifampin-resistant; RS, rifampin-susceptible; SOC, standard of care; TB, tuberculosis.

Table 3. Overall and Per-Test Impact of Different Approaches to Performing Fluoroquinolone Drug Susceptibility Testing Before Treating With the Novel Regimen, in South Africa and Southeast Asian Cohorts of 100 000 Individuals With Tuberculosis

Approach	South Africa ^a	Southeast Asia
FQ-DSTs performed		
No FQ-DST	0 (0–0)	0 (0–0)
Targeted FQ-DST	2060 (2030–2090)	2620 (2590–2650)
Universal FQ-DST	75 100 (75 000–75 200)	75 800 (75 700–75 800)
Cases of moxifloxacin resistance detected		
No FQ-DST	0 (0–0)	0 (0–0)
Targeted FQ-DST	162 (152–169)	300 (292–310)
Universal FQ-DST	354 (340–368)	1823 (1801–1857)
Percentage of overall TB cases cured		
No FQ-DST	89.2% (89.1%–89.3%)	89.2% (89.1%–89.3%)
Targeted FQ-DST	89.4% (89.3%–89.4%)	89.3% (89.2%–89.4%)
Universal FQ-DST	89.5% (89.4%–89.5%)	89.5% (89.4%–89.6%)
Moxifloxacin-resistant TB cases cured		
No FQ-DST	421 (411–437); 74% (73%–75%)	2508 (2466–2546); 81% (81%–82%)
Targeted FQ-DST	466 (453–487); 82% (81%–83%)	2570 (2549–2620); 83% (82%–83%)
Universal FQ-DST	496 (478–512); 86% (85%–86%)	2736 (2696–2783); 89% (88%–89%)
Incremental FQ-DSTs per incremental cure		
Targeted FQ-DST vs no FQ-DST	50 (42–70)	44 (37–51)
Universal FQ-DST vs targeted FQ-DST	3500 (2300–5500)	410 (370–450)
Universal FQ-DST vs no FQ-DST	1200 (1000–1400)	310 (300–340)

Unless otherwise indicated, data are shown as median (interquartile range) among 50 independent simulations of a cohort of 100 000 people with TB.

Abbreviations: DST, drug susceptibility testing; FQ, fluoroquinolone; TB, tuberculosis.

As a result, universal FQ-DST offered additional benefit in both settings: In South Africa, it increased cure of MFX-R TB to 85.7% (IQR, 84.9%–86.5%)—an absolute increase of 11.9% (IQR, 10.2%–13.2%) compared to no FQ-DST or 3.4% (IQR, 2.3%–5.4%) compared to RR-targeted FQ-DST. In South Asia, cure of MFX-R TB increased to 88.7% (IQR, 88.4%–89.0%)—increases of 7.5% (IQR, 6.9%–8.0%) compared to no FQ-DST and 5.8% (IQR, 5.1%–6.3%) compared to targeted FQ-DST, respectively. Overall TB cure also increased slightly in both settings (Table 2).

Expanding FQ-DST from a rifampin resistance–targeted strategy to universal testing was more efficient in Southeast Asia than in South Africa, reflecting the higher prevalence of fluoroquinolone resistance among people with RS-TB in Southeast Asia (Figure 2 and Table 3). In South Africa, expanding from targeted to universal FQ-DST required 3500 (IQR, 2300–5500) additional DSTs to effect 1 additional cure, compared with 410 (IQR, 370–450) in Southeast Asia. The impact and efficiency of expanding to universal FQ-DST differed similarly between settings when the outcome evaluated was the time spent with active, potentially transmissible MFX-R TB (Supplementary Figure 1).

Sensitivity Analyses

In 1-way sensitivity analysis, the yield of FQ-DST was highly sensitive to the projected efficacy of BPamZ (with the yield, eg, of targeted FQ-DST in South Africa ranging from 32 tests per additional cure at 2% relapse to 234 tests per cure at 12% relapse; Supplementary Figure 2). Results were also sensitive to

the modeled relationship between treatment duration and cure, and to the effects of additional drug resistance on recurrence risk (Supplementary Figure 2).

The burden of drug resistance in the population receiving DST was a major determinant of the impact and efficiency of FQ-DST, whether implemented in a targeted or universal manner (Supplementary Figures 2 and 3). The number of rifampin resistance–targeted DSTs required to produce 1 additional cure ranged from 11 (IQR, 10.8–11.3) in a cohort (resembling Belarus) with high levels of rifampin, moxifloxacin, and pyrazinamide resistance, to 2070 (IQR, 1020 to no predicted benefit) in a cohort where moxifloxacin and pyrazinamide resistance were as rare among patients with RR-TB as among South African patients with RS-TB (Supplementary Table 10).

The impact of FQ-DST also depended heavily on the robustness of the novel fluoroquinolone-containing regimen to the loss of fluoroquinolone activity. When we increased the importance of moxifloxacin by reducing the efficacy of BP_a and BP_aZ, the efficiency of RR-targeted FQ-DST in South Africa improved from 50 to 32 (IQR, 28–35) DSTs per additional cure achieved, and efficiency of universal FQ-DST improved similarly (Supplementary Figure 3).

When we increased the treatment duration from 4 months to 6 months for patients with RR-TB, the number of rifampin resistance–targeted FQ-DST tests required per additional cure increased from 50 to 140 (IQR, 90–250) in South Africa, and from 44 to 130 (IQR, 100–200) in Southeast Asia, with no change in

Figure 2. Impact of different approaches to fluoroquinolone drug susceptibility testing (FQ-DST) on treatment outcomes among people with moxifloxacin-resistant tuberculosis (TB) in South Africa and Southeast Asia. Different shadings represent different FQ-DST strategies. Results are restricted to patients with moxifloxacin-resistant TB (ie, those with potential to benefit from FQ-DST), who are shown divided by rifampin-susceptibility status (left and center) and then in aggregate (right). Box positions along the y-axis represent the absolute number of patients experiencing unsuccessful treatment (horizontal lines denoting medians, boxes denoting interquartile ranges, and error bars reflecting the full range of simulated outcomes). This absolute number reflects, in part, the size of the patient subgroup (greatest for rifampin-susceptible TB and overall moxifloxacin-resistant TB in Southeast Asia). Gray text shows the proportion of patients in each category who were unsuccessfully treated (highest among rifampin-resistant TB [RR-TB] in South Africa, where higher prevalence of pyrazinamide resistance increases the per-patient risk of unsuccessful treatment).

the incremental yield of expanding from rifampin resistance-targeted to universal DST.

DISCUSSION

Novel, fluoroquinolone-containing regimens that could treat both RR-TB and RS-TB would advance TB care, but implementing these regimens would benefit from a corresponding strategy for FQ-DST. Particularly for patients whose TB is rifampin-susceptible but fluoroquinolone-resistant—who comprise 50% of all fluoroquinolone-resistant TB in South Africa and >80% in Southeast Asia—using such a regimen without appropriate DST could worsen outcomes compared to the current standard of care. Our analysis shows that FQ-DST can augment the impact of novel regimens and improve patient outcomes, and identifies important setting-dependent and

regimen-dependent considerations for the design of locally appropriate DST strategies.

Pairing a new fluoroquinolone-containing regimen with universal FQ-DST will result in the best outcomes in all settings, but depending on the distribution of drug resistance, targeting DST to groups at highest risk for novel-regimen resistance (for example, patients with RR-TB or a history of prior TB treatment) may be far more efficient. In settings where a large proportion of fluoroquinolone-resistant TB is found among RR-TB—and where rifampin DST coverage is high, allowing for identification of the RR-TB population—restriction of FQ-DST to patients with RR-TB could be an effective, resource-conscious strategy. In South Africa, for example, an RR-targeted approach could identify nearly half as many patients with FQ resistance, while requiring <3% as many FQ-DST assays, relative to

a universal strategy. However, small absolute increases in the prevalence of fluoroquinolone resistance among RS-TB could considerably shift the relative efficiency of targeted vs universal DST approaches. When fluoroquinolone exceeded 3% in Southeast Asia, the per-test yield of universal DST drew near to that of a targeted approach, while potentially offering a simpler management algorithm and far greater overall impact.

In other epidemiological scenarios, these same principles could lead to other DST approaches. In parts of sub-Saharan Africa where very low levels of fluoroquinolone and pyrazinamide resistance can be confirmed [29, 30], novel regimen implementation without FQ-DST may be appropriate, at least during initial implementation. At the other extreme, in settings of very high drug-resistance prevalence, it could be advisable to perform universal FQ-DST and also to prescribe longer treatment durations whenever susceptibility to both pyrazinamide and moxifloxacin cannot be reliably confirmed.

Because DST will have the greatest impact when the prevalence of resistance is greatest, assessing the burden of drug resistance is a critical step in choosing a DST strategy. In our projections, if all TB patients received FQ-DST, the number of tests needed to cure 1 additional patient ranged from 1200 tests in South Africa (where <1% of all TB is moxifloxacin resistant), to 410 in Southeast Asia (4% moxifloxacin resistance), to 50 at the high levels of drug resistance (including >10% moxifloxacin resistance) found in some parts of Eastern Europe and Central Asia [10, 20, 31]. The burden of resistance to other novel regimen components (such as pyrazinamide) among fluoroquinolone-resistant TB also affected the impact of FQ-DST. Our analysis thus highlights the need for up-to-date drug susceptibility data from local epidemics in order to effectively implement new treatment options. To optimize strategic decision-making regarding DST implementation, data collection and reporting should include resistance to moxifloxacin, pyrazinamide, and novel drug classes among both RS-TB and RR-TB [10, 22, 32, 33], as well as the overlap between resistance to various drugs.

Besides epidemiologic factors, the optimal DST strategy may depend on the regimen being introduced. Less robust regimens will favor extending DST further into lower-risk subpopulations, because detecting unexpected drug resistance is more important when the costs of losing fluoroquinolone activity (in terms of increased treatment failure or acquired drug resistance) are greatest. Decision-makers may therefore need to consider preclinical and clinical data on subsets of a regimen (eg, on BP_a and BP_aZ, for the BP_aMZ regimen) together with their local epidemiology (eg, prevalence of pyrazinamide resistance) to judge how a regimen may perform in the context of unrecognized fluoroquinolone resistance. Reductions in regimen efficacy under programmatic conditions—and associated magnification of the impact of unrecognized drug resistance—may also increase the benefits of DST beyond our projections.

The robustness of the overall management strategy also merits consideration. Patients with identifiable risk factors for ancillary drug resistance may be managed more cautiously (eg, with the lengthened treatment duration currently being studied for RR-TB patients treated with BP_aMZ). These compensations for recognized risk increase the relative importance of testing for fluoroquinolone resistance where it is least suspected.

TB drug regimens, DST assays, and DST algorithms will continue to develop in parallel. The forthcoming Xpert XDR cartridge, with diagnostic accuracy results expected in early 2020, could integrate easily into existing TB diagnostic workflows. Using a second cartridge on the GeneXpert platform is particularly well-suited for stepwise DST strategies that target FQ-DST to patients with RR-TB, while future widespread use of fluoroquinolone-containing first-line regimens could justify integration of FQ-DST into the TB diagnostic step (as rifampin DST is now). Ongoing trials [6, 34, 35] will also provide guidance about the importance of incorporating targeted or universal DST for bedaquiline, clofazimine, nitroimidazoles, oxazolidinones, or other agents.

Our analysis has some important limitations. We modeled new drug combinations with which clinical experience remains very limited, requiring us to extrapolate treatment outcomes from early clinical data, animal data, and other TB treatment regimens. Our primary results correspond to a single estimate of regimen efficacy, and the uncertainty ranges shown do not capture the wide range of possible phase 3 trial outcomes for the BP_aMZ regimen. Sensitivity analyses indicate that variation in regimen efficacy could considerably change the quantitative estimates of yield per test, while having less effect on the relative yields of different strategies and in different settings. Our model does not incorporate transmission, nor does it fully capture the extent to which treatment of patients with undetected fluoroquinolone resistance will exacerbate selection of resistance to pyrazinamide and novel drugs. Thus, our projections are limited to the earliest years of novel regimen rollout, and they underestimate the importance of FQ-DST in preventing and detecting future drug resistance. Finally, our analysis does not explicitly incorporate costs, which will vary depending on DST implementation and resulting treatment modifications.

In summary, FQ-DST could have an important role in accompanying a novel fluoroquinolone-containing TB regimen, but decisions about its appropriate use involve setting- and regimen-specific considerations. DST will be most critical in populations among whom the burden of fluoroquinolone resistance is high, but even relatively low-risk patient subgroups may, in some settings, face sufficiently high risk of fluoroquinolone resistance to warrant DST. FQ-DST will also be especially important for a regimen whose efficacy depends heavily on the fluoroquinolone. In considering introduction of novel regimens and planning their implementation, national and local decision-makers may consider how their own drug resistance

epidemiology and DST capacity align with the scenarios we have illustrated.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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